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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/521,524	Applicant(s) DAVIDSON ET AL.	
	Examiner Shanon A. Foley	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8 and 10-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-8 and 10-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant is thanked for answering questions concerning the figures on December 13, 2001.

Continued Prosecution Application

The request filed on 11/30/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/521524 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-8 and 10-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 has been amended to recite the transitional phrase, "consisting essentially of". Independent claims 11, 17, and 22 also recite this claim language. It is clear from applicant's arguments that this transitional phrase has been inserted to specifically exclude the cre-lox recombination system because the system materially affects the basic and novel characteristics of the present invention.

However, after a careful and thorough review of applicant's arguments, reasoning, and citations of the case law, it is determined that the claim does not define the metes and bounds of what is specifically to be excluded or what would be considered to materially alter the plasmids in the claims. Since applicant specifically argues that the addition of cre-lox materially affects

the plasmids, the additional components in subsequent claims, such as incorporation of a gene of interest, substitutions, additions, deletions of E3, E4, and pIX regions, addition HSV Amplicon sequences, and addition of other sequences that allow integration into the host cell, also materially affect the plasmid compositions. Therefore, since it cannot be determined what is excluded or included from the claim language, the claims are vague and indefinite.

Claims 16, 17, and 22 state that the shuttle plasmid consists of Ad sequences 0 to 1. It is presumed that applicant intends for the shuttle plasmid to contain map units 0 to 1 and not just the first nucleotide. However, this presumption does not relieve applicant of the burden of amending the claim language to clearly define the invention.

Claim 15 is drawn to a shuttle plasmid comprising a novel promoter. A novel promoter has not been defined and it cannot be discerned what would constitute a novel promoter in the art.

Claim 22 is directed to a method for rapidly producing recombinant adenoviruses. Rapidly producing a product is relative and opinion-based with no definite metes or bounds. This rejection also affects dependent claims 23-25.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-8 and 10-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a cloning system and a method for making recombinant adenovirus consisting essentially of an adenovirus backbone plasmid consisting essentially of an adenovirus genome lacking specific map units and a shuttle plasmid consisting essentially of certain map units. Applicant has argued that the claims specifically exclude cre-lox recombinase because these components materially alter the plasmids. However, the claims do not specifically exclude any other ingredients or coding sequences that would also materially affect the individual components and it is not clear how cre-lox could materially alter the invention while other added components would not. There is no definition in the specification that would differentiate what is considered to be materially altering to the skilled artisan.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4, 5, 10, 11, and 13-25 rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al. (Molecular Medicine. 1999; 5: 224-231) and Chinnadurai et al. (Journal of Virology. 1979; 32 (2): 623-628.

The claims are drawn to a cloning system for generating recombinant adenovirus. The system contains two components. The first component is an of an adenovirus backbone plasmid consisting essentially of lacking map units 0-9.2 starting with the lefthand ITR. The second component is a shuttle plasmid consisting essentially of Ad map units 0-1 and 9.2 to 16.1. The system also consists of a deletion in E3.

Applicant argues that Aoki et al. does not teach the first or the second components consisting essentially of the particular map units because the reference includes cre-lox recombinase insertions within the plasmids which materially alter the plasmid content. The claim language selectively deletes these cre-lox insertions.

Applicant's arguments have been considered and a rejection is established to address the new scope of the claims.

Aoki et al. teaches a method for generating recombinant adenoviruses with two components. The first component is an adenovirus backbone plasmid lacking map units 0-9.2 starting with the lefthand ITR. The second component is a shuttle plasmid comprising Ad map units 0-1 and 9.2 to 16.1 and a gene of interest. Aoki et al also teaches a deletion in the E3 region, generation of the viruses in 293 cells that express E1, and further detects for the presence of wild-type virus. Aoki et al. does not teach a system for generating recombinant adenovirus without the cre-lox method.

However, Chinnadurai et al. teaches a method for generating recombinant adenovirus with homologous recombination between overlapping adenovirus sequences without using cre-loxP.

The method of Aoki et al. requires several method steps: constructing the plasmids, separately cre-treating the DNA to linearize the plasmids, recombining the plasmids for *in vitro* recombination, and transfecting the DNA into cells. In contrast, the method of Chinnadurai et al. comprises two method steps: digesting DNA and transfecting cells for *in vivo* assembly. One of ordinary skill in the art at the time the invention was made would have been motivated to use conventional homologous recombination techniques of Chinnadurai et al. because there are

fewer steps involved for making recombinant adenoviruses. One of ordinary skill in the art at the time the invention was made would have used specific map units taught by Aoki et al. in the recombinase method taught by Chinnadurai et al. et al. because Aoki et al. teaches that these map units can be recombined to propagate recombinant adenoviruses. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in combining the teachings of Chinnadurai et al. and Aoki et al. because the map units of Aoki et al overlap and homologous recombination would occur in the absence of cre-lox recombination. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 2, 3, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al. and Chinnadurai et al. as applied to claims 4, 5, 10, 11, and 13-25 above, and further in view of Krougliak et al. (Human Gene Therapy. 1995; 6: 1575-1586).

Applicant argues the teachings of Krougliak et al. combined with the teachings of Aoki et al. would yield an adenovirus that contains the left hand ITR and loxP sequences in the vector and shuttle plasmids.

Applicant's arguments have been considered, but are not found to be persuasive because the teachings of Aoki et al. combined with the teachings of Chinnadurai et al. render the incorporation of cre-lox obsolete. Also, the deletion of E4 or other regions enables the ordinary artisan to incorporate more genes into the adenovirus vectors. The adenovirus vectors of Krougliak et al. are only used to show motivation for deleting adenovirus regions since other ingredients and limitations in the claims, such as the left hand ITR, have been rendered obvious.

See the teachings of Aoki et al. and Chinnadurai et al. above. Neither reference teaches modifying E4.

Krougliak et al. teaches generating and propagating adenovirus with deletions in E3 and E4, see the first column on page 1576 and page 1585.

One of ordinary skill in the art at the time the invention was made would have been motivated to delete E3 and/or E4 to insert more transgenes and because Krougliak et al. teaches that E3 deletions do not affect viral growth properties in culture, see the first paragraph on page 1576 and E4 deleted adenovirus vectors are very attenuated and are safer for gene therapy protocols, see page 1585. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Krougliak et al. teaches the specific map units that are to be deleted and these sites do not overlap or include the overlapping map units of Aoki et al. so that homologous recombination, taught by Chinnadurai et al. will take place. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al., Chinnadurai et al., and Krougliak et al. as applied to claims 2-6, 10, 11, and 13-25 above, and further in view of Breakfield et al. (5,965,441).

The claims are drawn to the cloning system further comprising genes required for Herpes Simplex Virus (HSV) packaging and an HSV origin of replication inserted in the E3 region and the backbone plasmid comprising HSV Amplicon sequences.

Applicant argues that the combination of Aoki et al. and Krougliak et al. would yeild an adenovirus with loxP, AAV/HSV hybrid sequences, and the left-hand ITR.

As discussed above, the combined teachings of Aoki et al. and Chinnadurai et al. render the incorporation of cre-lox obsolete and the teachings of Breakfield are incorporated to show motivation to add an HSV amplicon to Aoki's backbone plasmid.

See the teachings of Aoki et al., Chinnadurai et al., and Krougliak et al. above. None of the references teach incorporating an HSV Amplicon sequences.

However, Breakfield et al. teaches hybrid vector constructs that comprise an HSV Amplicon, see figure 1 in column 3, lines 50-65, and column 7, lines 35-38. Breakfield et al. teaches that the adenoviruses and AAV can generate long-term gene expression in post-mitotic cells, but not mitotic cells without the aid of the amplicon, see column 5, lines 26-36.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate HSV Amplicon sequences in to the backbone of Aoki et al. to expand the host range of gene expression to dividing cells. Breakfield et al. teaches expression in dividing and non-dividing cells, see column 10, lines 39-67 and column 11, lines 1-10 with the AAV hybrid. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Krougliak et al. teaches that deletion of E3 does not affect virus propagation in cell culture and replacement of E3 with the HSV amplicon sequences would not affect the overlapping sequences of Aoki et al. required for homologous recombination of Chinnadurai et al. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art absent unexpected results.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al. and Chinnadurai et al. as applied to claims 4, 5, 10, 11, and 13-25 above, and further in view of Chartier et al. (Journal of Virology. 1996; 70 (7): 4805-4810).

Applicant incorporates previous arguments regarding the left hand ITR and the loxP sites that have been previously addressed.

The claim is drawn to flanking either end of the Ad sequences with *Pac*I restriction sites.

Neither Aoki et al. nor Chinnadurai et al. teach incorporating *Pac*I restriction sites.

However, Chartier et al. teaches that *Pac*I is absent in Ad5 genomic DNA and allows for the precise excision of the gene of interest, see the paragraph bridging pages 4806-4807, figure A on page 4806, figure 2 on page 4808.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate a unique restriction site within the adenovirus shuttle plasmid of Aoki et al. to enable obtain a wider choice of cloning sites within the adenovirus genome. One of ordinary skill in the art at then time the invention was made would have had a reasonable expectation of producing the claimed invention because *Pac*I can be inserted into the shuttle of Aoki et al. by conventional methods.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SAF

Shanon Foley/SAF
December 15, 2001

James C. Housel

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